UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/498,135	02/04/00	STONE J	36435.0100

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HM22/0326

EXAMINER	
GOLDBERG, I	
ART UNIT	**PAPER NUMBER**
1655	10

DATE MAILED: 03/26/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action	Application No. 09/498,135	Applicant(s) STONE, JOHN F.	
	Examiner Jeanine A Enewold Goldberg	Art Unit 1655	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 13 March 2001 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ In view of the early submission of the proposed reply (within two months as set forth in MPEP § 706.07 (f)), the period for reply expires on the mailing date of this Advisory Action, OR continues to run from the mailing date of the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will be entered upon the timely submission of a Notice of Appeal and Appeal Brief with requisite fees.

3. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search. (see NOTE below);

   (b) ☐ they raise the issue of new matter. (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

4. ☐ Applicant's reply has overcome the following rejection(s): _____.

5. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

6. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

7. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

8. ☒ For purposes of Appeal, the status of the claim(s) is as follows (see attached written explanation, if any):

   Claim(s) allowed: *NONE*.

   Claim(s) objected to: *NONE*.

   Claim(s) rejected: *1-17*.

   Claim(s) withdrawn from consideration: *NONE*.

9. ☐ The proposed drawing correction filed on _____ a)☐has b)☐ has not been approved by the Examiner.

10. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

11. ☐ Other:

Continuation of 6. does NOT place the application in condition for allowance because:

103 Rejections over Cherry in view of Marcon-
The response asserts that Cherry does not teach analysis of the nucleic acid in interphase cells. The response asserts that Marcon does not discuss disease diagnosis. The response asserts that Marcon only teaches analysis of specific chromosomes in targeted areas. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The combination of Cherry and Marcon would suggest disease diagnosis in interphase cells. As previously stated, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cherry to predict the AD state of individuals with the method of Marcon for determining chromosome damage in interphase cells. The ordinary artisan would have been motivated to have analyzed interphase cells using the method of Marcon for the expected benefits of the feasibility of using this approach to simultaneously investigate different cell types (pg 156, col. 2) including those different cell types including those not amenable for metaphase analysis, and further, "this allows cells with different metabolic capabilities and turn-over, or the same cell population in different phases of the cell cycle, to be studied" (pg 164, col. 1). The ordinary artisan would have realized that expanding the method of Cherry to include studying interphase cells as taught by Marcon would vastly increase the information gained with respect to the chromosome breakage in a cell.

The response asserts that the two references are nonanalogous and not combinable. In response to applicant's argument that Cherry and Marcon are nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, both Cherry and Marcon are directed to analysis of chromosome breakage. Cherry is directed to disease diagnosis based upon chromosome breakage wheras Marcon is directed to the interphase and metaphase analysis of chromosome breakage. The response asserts that nothing in either Cherry or Marcon teaches or suggest the combination of the two references. The ordinary artisan would have recognized at the time of filing that both interphase and metaphase cells may be analyzed for chromosome breakage, as taught by Marcon and Cherry respectively. The ordinary artisan would have also realized that disease diagnosis was facilitated by the analysis of chromosome breakage, as taught by Cherry. The ordinary artisan would have combined the teachings of Cherry, for diagnosis of AD by detection of chromosome breaks, with the teachings of Marcon that analysis of chromosome breaks in interphase cells had many added benefits, as provided above. There would have been a reasonable expectation of success that the ordinary artisan would have been able to induce chromosome damage in interphase cells for the purpose of disease diagnosis.

The response asserts that Marcon does not teach labeling the ends of chromosome fragments. This argument has been reviewed but is not convincing because the claims are not specifically directed to labeling ends of choromsome fragments.

The response suggests that Cherry nor Marcon disclose or suggest 3'-OH strands, however, Cherry specifically teaches that Bleomycin induces damage through the generation of activated oxygen and hydroxyl radical with the cell. In the case of bleomycin, these radicals tend to attach the C-5 position of the deoxyribose sugar ring causing breakage of the ring and releas of the pyrimidine base. Thus, as pointed out in the Office Action mailed 12/14/00 on page 3, line 6, Cherry teaches producing 3'- OH strands (pg 64, col. 1).

103 Rejection over Chen in view of Marcon-
The response asserts that Chen does not teach analysis of the nucleic acid in interphase cells. The response asserts that Marcon does not discuss disease diagnosis. The response asserts that Marcon only teaches analysis of specific chromosomes in targeted areas. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The combination of Chen and Marcon would suggest disease diagnosis in interphase cells. As previously stated, it would have been obvious to of ordinary skill in the art at the time the invention was made to have modified the method of Chen to predict the AD state of individuals with the method of Marcon for determining chromosome damage in interphase cells. The ordinary artisan would have been motivated to have analyzed interphase cells using the method of Marcon for the expected benefits of the feasibility of using this approach to simultaneously investigate different cell types (pg 156, col. 2) including those different cell types including those not amenable for metaphase analysis, and further, "this allows cells with different metabolic capabilities and turn-over, or the same cell population in different phases of the cell cycle, to be studied" (pg 164, col. 1). The ordinary artisan would have realized that expanding the method of Chen to include studying interphase cells as taught by Marcon would vastly increase the information gained with respect to the chromosome breakage in a cell. The ordinary artisan would have realized that expanding the method of Chen to include studying interphase cells as taught by Marcon would vastly increase the information gained with respect to the chromosome breakage in a cell.

103 Rejection over Parshad in view of Marcon-
The response asserts that Cherry does not teach analysis of the nucleic acid in interphase cells. The response asserts that Marcon does not discuss disease diagnosis. The response asserts that Marcon only teaches analysis of specific chromosomes in targeted areas. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The combination of Cherry and Marcon would suggest disease diagnosis in interphase cells. As previously stated, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Prashad to predict the AD state of individuals with the method of Marcon for determining chromosome damage in interphase cells. The ordinary artisan would have been motivated to have analyzed interphase cells using the method of Marcon for the expected benefits of the feasibility of using this approach to simultaneously investigate different cell types (pg 156, col. 2) including those different cell types including those not amenable for metaphase analysis, and further, "this allows cells with different metabolic capabilities and turn-over, or the same cell population in different phases of the cell cycle, to be studied" (pg 164, col. 1). The ordinary artisan would have realized that expanding the method of Prashad to include studying interphase cells as taught by Marcon would vastly increase the information gained with respect to the chromosome breakage in a cell. Thus, based upon the teachings in Prashad that significant differences between AD and controls were observed when cells were treated with radiation and caffeine (pg. 5147, col. 2), the ordinary artisan would have been motivated to test unknown interphase samples to determine the AD status of the individual.

The response suggests that Prashad nor Marcon disclose or suggest 3'-OH strands, however, Prashad teaches the lymphocyte cultures were subjected to either fluorescent light or 254 nm UV light (chromosome damaging agent that causes free radical-induced DNA damage) (pg. 5147, col. 1, para. 3 and 4)(limitations of Claim 6). Moreover, the cells were then treated with beta-cytosine arabinoside (araC) or caffeine (repair retarding agents) (limitations of

Claim 5 and 12). Thus, as pointed out in the Office Action mailed 12/14/00 on page 7-8, lines 1-3, Cherry teaches producing 3'- OH strands.

103 Rejection over Cherry, Marcon and Gorczyca-
The response asserts that the teachings of Gorczyca with regard to apoptosis is not a disease state. This argument has been reviewed but is not convincing because the teachings of Gorczyca have not been used to demonstrate the diagnosis of a disease. The teachings of Gorczyca illustrate numerous means by which chromosome breaks may be analyzed. Apoptosis while not a disease state, per se, is involved in many disease states such as cancers. The chromsome breaks of the instant study, however, are a result of exposure to drugs. Regardless, Gorczyca specifically states that the response of human leukemisa to various drugs can be monitored with the TdT assay, implying that Gorczyca is indirectly diagnosis of disease state.

Finally, the reponse asserts that the Examiner did not state why the depended claims were not allowable over the cited references and request withdraw of finality. This argument has been reviewed but is not convincing because the dependent claims have been each addressed and noted with "limiations of Claim *" following the passage to which they relate. The Examiner has expressly pointed out where 3'-OH and repair retarinding agents were taught, see discussion of rejections above.

In summary, it is the Examiner's position that given the teachings in the art, Cherry, Chen, Prashad, Marcon and Gorczyca, the instant claims would have been obvious to one of ordinary skill in the art. Cherry, Chen, Prashad all teach diagnosising disease based upon the number or frequency of chromosome breaks in metaphase cells. Marcon teaches that analysis of chromosome breaks can be performed on interphase cells with additional benefits, thus indicating that interphase analysis of chromosome breaks is preferential to metaphase cells. Thus, the skilled artisan would have modified the teachings of any of Cherry, Chen, Prashad to analyze interphase cells for the benefits of Marcon. Moreover, Gorczyca teaches that broken ends of DNA can be labeled with TdT or NT assays. Therfore the combination of the cited references provide a reasonable expectation of success that the ordinary artisan could expose interphase cells (as taught by Marcon) of a patient with AD to a damaging agent (as taught by Cherry, Chen or Prashad), mark the fragments (as taught by Gorczyca) to determine whether the cells are affected by the disease (as taught by Cherry, Chen, Prashad).

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3/23/01